UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte KUBER T. SAMPATH,
SHUN-ICHI HARADA, and GIDEON A. RODAN,

Appeal No. 2006-0882
Application No. 09/613,177

ON BRIEF

Before ADAMS, MILLS, and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to a method for identifying compounds that induce biological effects which are normally mediated by morphogenic proteins. The examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 134. We reverse.

Background

Morphogenic proteins include "the class of proteins typified by human osteogenic protein 1 (hOP-1). hOP-1 and functionally equivalent morphogens are dimeric proteins that induce uncommitted cells of mammalian origin to undergo a cascade of cellular and molecular events that culminates in the formation of functional, differentiated

mammalian tissues, e.g., bone, liver, nerve, tooth dentin, periodontal tissue, gastrointestinal tract lining tissue, and the like." Specification, pages 3-4. Because of their involvement in the formation of specific tissues, morphogenic proteins, or "morphogens," are the focus of efforts directed to putting the proteins to therapeutic uses, such as healing injured or diseased bone tissue. Page 2.

The specification discloses that analogue compounds inducing effects similar to those of morphogens can be identified by providing a test cell comprising a transcription activating element which is responsive to OP-1, or a related morphogen, wherein the transcription activating element is operatively linked to a reporter gene. Page 4. Contacting the cell with a candidate compound can determine whether the candidate has biological activity similar to a morphogen by detecting expression of the reporter gene. Specification, pages 4-5.

Discussion

1. Claim construction

Claims 1-10, 13, 15, 30-33, 36 and 43-50 are pending. Of these, claims 15 and 30-32 have been allowed. Office Action of April 28, 2005, page 2. Claims 4, 5, 7, 8, 10 and 33 are objected to as depending from rejected claims. Id. Claim 48, initially part of this appeal, was subject to a rejection which has been withdrawn by the examiner, and remains objected to as depending from a rejected claim. Answer, page 2.

Claims 1-3, 6, 9, 13, 36, 43-47, 49 and 50 are therefore the subject of this appeal.

The broadest claim on appeal, claim 1 reads as follows:

1. A method for identifying a compound that induces a morphogen-mediated biological effect, the morphogen selected from OP-1, OP-2, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-9, Vg1, Vgr-1, DPP, or 60A, the method comprising:

(a) providing a test cell comprising a DNA comprising:

(i) a transcription activating element that is responsive to, and distinct from the gene encoding, said morphogen, and

(ii) a reporter gene encoding a detectable gene product, the transcription activation element being in operative association with the reporter gene,

wherein the reporter gene is transcribed when the DNA is present in a cell that is

(1) responsive to the morphogen, and

(2) contacted with said morphogen;

(b) exposing said test cell to a candidate compound; and

(c) detecting expression of said detectable gene product, wherein an increase in expression of said detectable gene product after exposing said test cell to said candidate compound indicates the ability of the compound to induce the morphogen-mediated biological effect;

wherein said morphogen-mediated biological effect requires the presence of said transcription activating element, so as to thereby identify a compound that induces a biological effect mediated by a morphogen.

Thus, claim 1 is directed to a method of identifying a compound capable of inducing a biological effect mediated by any one of twelve enumerated morphogens. By exposing a test cell to a candidate compound, the candidate compound's ability to induce a morphogen-mediated biological effect can be assessed by detecting the expression of a reporter gene product in a test cell.

The claim requires the reporter gene to be in operative association with "a transcription activating element that is responsive to, and distinct from the gene encoding, said morphogen." The "transcription activating element" must therefore be distinct from a gene encoding a morphogen. However, because the reporter gene is operatively associated with a DNA sequence that is responsive to a morphogen, expression of the reporter gene indicates that the candidate compound activates expression of the gene linked to the same element that is activated by the morphogen. Thus, the candidate compound would be expected to induce a biological effect mediated by a morphogen.

2. Obviousness

The examiner rejected claims 1-3, 6, 9, 13, 36, 43-47, 49 and 50, under 35 U.S.C. § 103 on the basis that the claimed subject matter would have been obvious in view of Harris,[1] Smart[2] and Nadal-Ginard.[3]

The examiner cited Harris for its teaching of a method for identifying a compound that induces a morphogen mediated biological effect. Answer, page 3. The examiner pointed out that Harris' methods involve contacting a candidate compound with a test cell containing a promoter element operatively linked to a reporter gene, wherein increased production of reporter gene product is indicative of the candidate compound's ability to induce a morphogen-mediated biological effect. Id., at pages 3-5. The examiner noted that Harris contemplated the use in the disclosed assay method of

[1] Harris et al., U.S. Patent 6,083,690, issued July 4, 2000 (filed June 2, 1995).
[2] Smart et al., U.S. Patent 5,650,276, issued July 22, 1997 (filed July 20, 1994).
[3] Nadal-Ginard et al., WO 94/18239, published August 18, 1994.

promoters "from genes including BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, as well as similar genes." Id., at page 4, citation omitted.

The examiner acknowledged that "[w]hile Harris expressly recognizes that the promoters from other, similar, genes can be used in the screening method, Harris does not specifically teach the use of the OP-1 gene." Id., at page 6. To meet this limitation, the examiner relied on Smart's teaching of "the desirability of screening candidate compounds for their ability to modulate morphogenic proteins" including OP-1 and OP-2. Id.

The examiner then acknowledged that "Harris in view of Smart do not teach the use of the MEF-2 or AP-1 elements, which are functional in muscle cells." Id. The examiner cited Nadal-Ginard as teaching methods of "screening for agents which either enhance o[r] decrease the interaction of MEF2 transcription factors as well as MyoD and MASH transcription factors." Id., at page 7. We note that claim 1 does not require the "transcription activating element" to bind to MEF-2. However, dependent claim 2 recites that the "transcription activating element [of claim 1] binds with a protein having general DNA-binding properties of a MEF-2 family protein." Claim 3 also requires that the "transcription activating element comprises a sequence that hybridizes to an MEF-2 binding site sequence." Thus, the examiner in effect relied on Nadal-Ginard's disclosure to meet the limitation in claim 1 of "DNA comprising . . . a transcription element that is responsive to, and distinct from the gene encoding, said morphogen."

As motivation for combining the teachings of Harris and Smart, the examiner noted that Harris suggested the use of "other promoters" in the disclosed methods of screening for morphogenic activity, and concluded that "an ordinary practitioner, faced

with the teaching of Harris that other promoters are of interest, would have been expressly motivated by Smart to study OP-1, which is shown by Smart as an important morphogenic protein." Id. Thus, argued the examiner, one of ordinary skill motivated by Smart to identify morphogenic compounds would have been further motivated by Harris to have applied Harris' methods "since Harris expressly suggests analysis of such pathways [of morphogenesis] and since Harris clearly indicates that such screening can result in clinical and therapeutic advantages." Id.

To provide motivation for combining Nadal-Ginard with Harris and Smart, the examiner relied on Nadal-Ginard's teaching that agents identified therein would increase or decrease the interaction between tissue-specific transcription factors including MEF-2, and a "pocket protein" required for activity of those transcription factors. Id., at page 8. The examiner further relied on Nadal-Ginard's teaching that the discovery of the requirement for interaction between the pocket protein and transcription factors "provides the basis for screening therapeutic agents useful for regulating the switch between the cell's growth phase and a terminally differentiated state." Id. (quoting Nadal-Ginard at page 4, lines 18-20). Thus, urged the examiner, "an ordinary practitioner would have been motivated by Nadal-Ginard to screen for compounds which are involved in differentiation using the MEF2 transcription sites in view of Nadal-Ginard's express motivation to use these enzymes in screening between differentiation and growth." Id.

Appellants argue that the combination of Harris, Smart, and Nadal-Ginard fails to teach all limitations present in the claims. Brief, pages 4-7; Reply Brief, pages 2-4. Appellants specifically urge that "[t]he combination of the cited references . . . fails to

teach or suggest a transcription activating element ('TAE') that is (1) distinct from the gene encoding said morphogen and (2) responsive to the morphogen for screening compounds." Brief, page 5. Appellants further argue that "[t]he Examiner has failed to show a motivation or suggestion to combine Harris with Smart, or Harris/Smart with Nadal-Ginard." Brief, page 7.

As stated in In re Fritch, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (citations omitted), "the examiner bears the burden of establishing a prima facie case of obviousness based on the prior art. '[The Examiner] can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.'" Thus, "identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant." In re Kotzab, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000) (citation omitted).

We note that "the Board need only establish motivation to combine by a preponderance of the evidence to make its prima facie case." In re Kahn, 441 F. 3d 977, 989, 78 USPQ2d 1329, 1338 (Fed. Cir. 2006), citing In re Glaug, 283 F.3d 1335, 1338, 62 USPQ2d 1151, 1152-53 (Fed. Cir. 2002). However, in our view, the examiner has not established by a preponderance of the evidence that the claimed subject matter would have been prima facie obvious.

To rebut Appellants' argument regarding lack of motivation, the examiner notes that Nadal-Ginard's assay methods allow for identifying therapeutic agents capable of "regulating the switch between the cell's growth phase and a terminally differentiated state." Answer, page 12 (quoting Nadal-Ginard at page 4, lines 18-20). The examiner thus ties together the argument for motivation by stating (Answer, pages 12-13, citations omitted):

> Therefore, the ordinary practitioner was taught by Nadal-Ginard that transcription activating elements distinct from the gene of interest could be used in screening for therapeutic agents, and Nadal-Ginard motivates such a use in order to identify interactions with the transcription factor and permitting identification of compounds which regulate the switch between the cell's growth phase and terminally differentiated state, or morphogens in the vernacular of the specification. In combination with the teaching of Harris that the BMP proteins (and the teaching of Smart that the OP-1 protein) are proteins of interest for screening for therapeutic agents associated with regulation of cell growth and differentiation, Nadal-Ginard teaches identification of agents where the transcription activating element is responsive to, but distinct from the gene encoding the morphogen, where the morphogen may be a BMP protein or OP-1.

We do not find the examiner's argument persuasive. Specifically, the examiner fails to provide a specific link between Nadal-Ginard's teachings and the morphogenic proteins assayed in Harris and Smart, such that one of ordinary skill assaying for the morphogens taught by Harris and Smart would have been motivated to have used Nadal-Ginard's methods.

We agree with the examiner (Answer, page 12) that the morphogens assayed in Harris and Smart are involved in cell differentiation. Moreover, we agree with the examiner (Answer, page 11) that Nadal-Ginard's failure to use the term "morphogen" does not diminish the reference's teaching of methods of assaying for agents which

affect differentiation. See, e.g., Nadal-Ginard, abstract. However, other than their common association with differentiation events, the examiner does not point to anything in the references which would have suggested to the artisan of ordinary skill that the largely bone cell-related morphogenic proteins of Harris and Smart would act on, or bind to, the MEF-2 binding sequences that are disclosed by Nadal-Ginard as being active in muscle cells. Nadal-Ginard, e.g., at page 4, lines 5-7. Similarly, the examiner does not point to anything specific in the prior art to suggest that the morphogens of Harris or Smart interact with the pocket protein used in Nadal-Ginard's assays.

In our view, the cited references' common theme of identifying compounds which modulate differentiation, cited by the examiner as providing motivation for combining the references, at best suggested that the artisan of ordinary skill might try the assay methods described in Nadal-Ginard, to see if they would be capable of identifying compounds which induce biological effects mediated by the morphogens described in Harris and Smart. However, such an invitation to experiment does not rise to the level of obviousness. See In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988) ("'[O]bvious to try' is not the standard under § 103.").

Specifically, "[a]n 'obvious-to-try' situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." In re Eli Lilly & Co., 902 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990). Thus, one of ordinary skill viewing the cited references may have recognized from Nadal-Ginard that MEF-2-responsive DNA sequences could have

been used in assays for compounds affecting differentiation events (see Nadal-Ginard, e.g. at pages 9 and 64). However, the examiner has failed to establish a recognition in the prior art that the specific morphogens of Harris and Smart, recited in claim 1, would have acted on the promoter elements in Nadal-Ginard. Therefore, in our view, the proposed combination of references would have made the instantly claimed method, at best, obvious to try. We therefore reverse this rejection.

Other Issues

In University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1405-1406 (Fed. Cir. 1997), the court held that a patent specification's disclosure of a single cDNA sequence encoding rat insulin did not provide an adequate written description under 35 U.S.C. § 112, first paragraph, for claims generically reciting DNA sequences encoding vertebrate or mammalian insulin cDNA. ("[I]t is clear to us, as it was to the district court, that the claimed genera of vertebrate and mammal cDNA are not described by the general language of the '525 patent's written description supported only by the specific nucleotide sequence of rat insulin.")

In the case before us, claim 1 generically recites "DNA comprising . . . a transcription element that is responsive to, and distinct from the gene encoding, said morphogen." Appellants' specification appears to disclose the DNA sequence of only one such transcription activating element, a sequence within the mouse type X collagen gene promoter. See, e.g., Specification, pages 36-41 (Example 2). It is not clear from the record whether other DNA sequences responsive to, and distinct from, the genes of the claimed morphogens were known in the art. Our review of the prosecution history

does not indicate that the examiner has addressed the issue of whether the specification provides a sufficient written description of the transcription activating element generically defined in claim 1. Therefore, when the examiner takes this case up for action, the examiner should consider whether, in light of the decision in University of California v. Eli Lilly, and other recent case law, the specification provides a sufficient written description for the transcription activating element generically recited in the claims.

In addition, we note that claim 6 contains the recitation "said morphogen activating element." Claim 6 depends from claim 1. Neither claim 6 nor claim 1 recites a "morphogen activating element." The recitation "said morphogen activating element" therefore lacks clear antecedent basis in the claims. Also, the recitation is confusing in the context of the claims, since the "transcription activating element" (emphasis added) central to this case is activated by a morphogen, and not the other way around. We note that this error appears to have occurred when Appellants, perhaps inadvertently, failed to delete the term "morphogen" from claim 6 when making the amendment of February 22, 2005. When the examiner takes this case up for action this definiteness issue should also be addressed.

Summary

The examiner has not established a prima facie case of obviousness based on the Harris, Smart and Nadal-Ginard references. We therefore reverse the obviousness rejection over those references.

We also recommend that the examiner consider whether the specification provides a written description, under 35 U.S.C. § 112, first paragraph, for the transcription activating element recited in the claims. The examiner should also review the claims, especially claim 6, for definiteness.

REVERSED

Donald E. Adams)
Administrative Patent Judge)
)
)
Demetra J. Mills) BOARD OF PATENT
Demetra J. Mills)
Administrative Patent Judge) APPEALS AND
)
) INTERFERENCES
)
Eric Grimes)
Administrative Patent Judge)

EG/dm

Fish & Neave IP Group
Ropes & Gray LLP
One International Place
Boston, MA 02110-2624